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Diastrophic Dysplasia: Extreme Variability Within a Sibship

Bryan D. Hall
Department of Pediatrics, University of Kentucky, Kentucky Clinic, Lexington, Kentucky

Three sibs were eventually diagnosed as having diastrophic dysplasia. The firstborn, a male, lacked many of the clinical manifestations and radiological abnormalities of the hands, such that the diagnosis of diastrophic dysplasia could not be made. Subsequently, his twin sisters were born with more severe skeletal involvement, but not many additional clinical findings, until one of his sisters (patient 2) developed a left ear cyst at age 2 months. Some cases of diastrophic dysplasia may be mild enough not to allow for a secure diagnosis, particularly in a neonate or infant occurring as the first affected person in the family.

KEY WORDS: diastrophic dysplasia, dwarfism, variability, ear cyst

INTRODUCTION

Diastrophic dysplasia is an autosomal-recessive skeletal dysplasia with a unique pattern of abnormalities, originally described by Lamy and Maroteaux [1960]. It includes disproportionate short stature, talipes equinovarus, flexion contracture of the knees, increased incidence of dislocation at major joints, "hitchhiker thumb" due to a short first metacarpal, cystic/cauliflower ear abnormalities, cleft palate, and progressive scoliosis [Lachman et al., 1981]. However, enough variability exists that some patients were labeled "diastrophic variant," which prompted some authors [Horton et al., 1978; Lachman et al., 1981] to report sibships with significant variability. Lachman et al. [1981] correctly decreed "death" to the variant. Review of other papers [Walker et al., 1972; Kaitila et al., 1989] demonstrated wide variability in some sibships, further supporting the concept of "death" to the variant.

The issue of this paper is that variability can be such as to miss the diagnosis of diastrophic dysplasia, particularly if the first affected in a sibship is mildly affected or lacks a number of the more frequent findings. A firstborn affected male, and subsequently born affected MZ twin sisters, are presented for consideration of the validity of this potential dilemma.

CLINICAL REPORTS

The parents were sixth or seventh cousins. None of the 3 pregnancies were complicated and there was no teratogenic exposure. The 3 children are the only ones born to this couple. At time of birth of the affected male (patient 1), the father was 26 and the mother was 17 years old. Table I shows the birth parameters of the 3 affected sibs. Note that the male (patient 1) had a normal birth length (25th centile), while the twin girls (patients 2 and 3) fell below the 3rd centile despite weight at the 25th centile. Table II shows the growth parameters when the boy (patient 1) was 2½ years old and his twin sisters (patients 2 and 3) were 2½ months old. All 3 children were then below the 3rd centile in length. Table III documents the clinical findings of all 3 affected sibs. The boy's only joint problem (Fig. 1) was bilateral talipes equinovarus; he lacked clinocamptodactyly and flexion crease hypoplasia of the fingers. The twin sisters (Fig. 2) also had bilateral talipes equinovarus without other joint involvement. They and their brother had ears "on the thick side," but otherwise normal auricle. At age 2 months, one of the twin girls (patient 2) developed a cyst of the left ear (Fig. 3) involving the anterior and superior helix. Both twins had clinocamptodactyly and hypoplastic finger flexion creases (Fig. 4), but neither had thumb abnormalities. The twins also had more marked ulnar deviation of the hand at the wrist than their older brother. Note that all 3 sibs lacked cleft palate, ear cyst (except for patient 2), hitchhiker thumb, joint dislocations, knee contractures, pretibial dimples, and scoliosis. Table IV presents the radiological findings in the

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Address reprint requests to Bryan D. Hall, M.D., Department of Pediatrics, University of Kentucky, Kentucky Clinic, Lexington, KY 40536-0284.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

TABLE I. Birth Parameters in a Sibship With Diastrophic Dysplasia

	Male, patient 1	Female, twin A, patient 2	Female, twin B, patient 3
Gestation (weeks)	31	32	32
Birth length (cm, centile)	38, 25th	35, <3rd	34, <3rd
Birth weight (g, centile)	1,590, 25th	1,400, 25th	1,405, 25th
Birth head circumference (cm, centile)	28, 30th	29, 25th	29.25, 35th

TABLE II. Growth Parameters in Sibship With Diastrophic Dysplasia

	Male, patient 1	Female, twin A, patient 2	Female, twin B, patient 3
Age	2½ years	2½ months	2½ months
Length (centile)	<3rd	<3rd	<3rd
Weight (centile)	10th	<3rd	<3rd
Head circumference (centile)	25th	<3rd	<3rd

3 sibs. The brother's (patient 1) neonatal films showed mild shortness and bowing of the long bones with short femoral necks, straight spine, and thin ribs (Fig. 5). At age 10 months, the long bones were shorter and thicker with wide metaphyses (Figs. 6, 7). The boy's hand showed generalized brachydactyly with regular configuration of the phalanges and metacarpals, without disproportionate shortness or ovoid formation of the first metacarpal (Fig. 8). The twin sisters' (patients 1 and 2) radiological findings were similar, but more severe in infancy, with short, bowed long bones and wide metaphyses (Fig. 9) and somewhat greater hand involvement (Fig. 10).

DISCUSSION

Initially, the firstborn child (patient 1) was considered to have an unknown bone dysplasia. Diastrophic dysplasia was considered, but because he lacked cleft palate, ear cyst, hitchhiker thumb/short ovoid first metacarpals, clinocamptodactyly of the fingers, finger flexion crease hypoplasia, joint dislocations, knee contractures, pretibial dimples, or scoliosis, it was thought he could not be diagnosed as having diastrophic dysplasia. After the birth of his more severely affected twin sisters, particularly after one of the sisters developed a "pathognomonic" ear cyst, the diagnosis of diastrophic dysplasia became obvious in the boy as well. It should be noted that the twin sisters also lacked some of the major clinical anomalies of diastrophic dysplasia, but had more severe skeletal involvement without irregular phalanges and metacarpals and short/ovoid first metacarpals.

The prematurity in all 3 affected sibs and the twinning in the sisters could have affected the clinical and radiological phenotype to some undetermined degree.

TABLE III. Clinical Findings in a Sibship With Diastrophic Dysplasia

	Male, patient 1	Female, twin A, patient 2	Female, twin B, patient 3
Prominent forehead	+	+	+
Micrognathia	+	+	+
Mildly thick ears	+	+	+
Pectus excavatum	+	–	–
Clinocamptodactyly	–	+	+
Absent flexion creases	–	+	+
Ulna hand angulation	+	++	++
Talipes equinovarus	+	+	+
Cleft palate	–	–	–
Ear cyst	–	+ (onset, age 2 months)	–
Hitchhiker thumb	–	–	–
Knee contractures	–	–	–
Pretibial dimple	–	–	–
Scoliosis	–	–	–

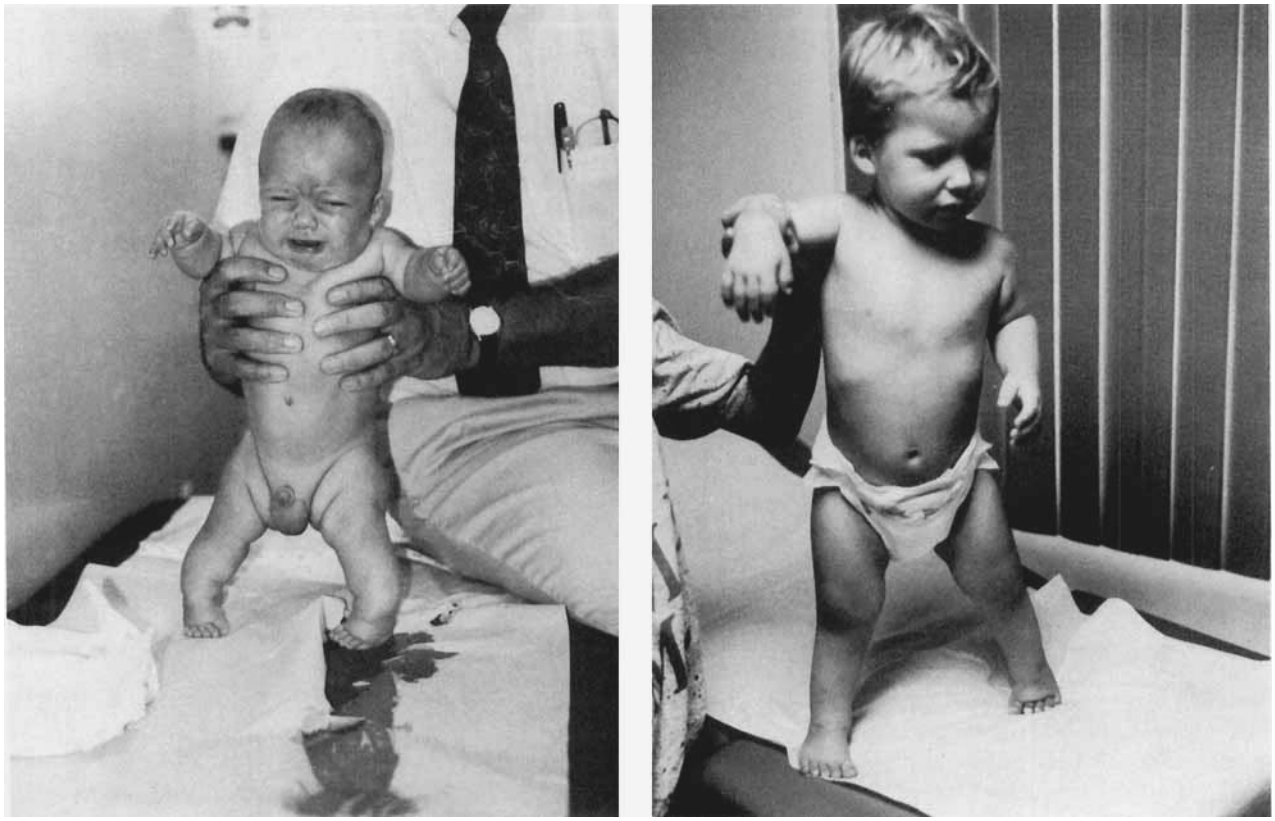

Fig. 1. Patient 1 at age 4 months (**left**) and 2½ years (**right**). Note talipes equinovarus (left), short limbs, and lack of other joint contractures.

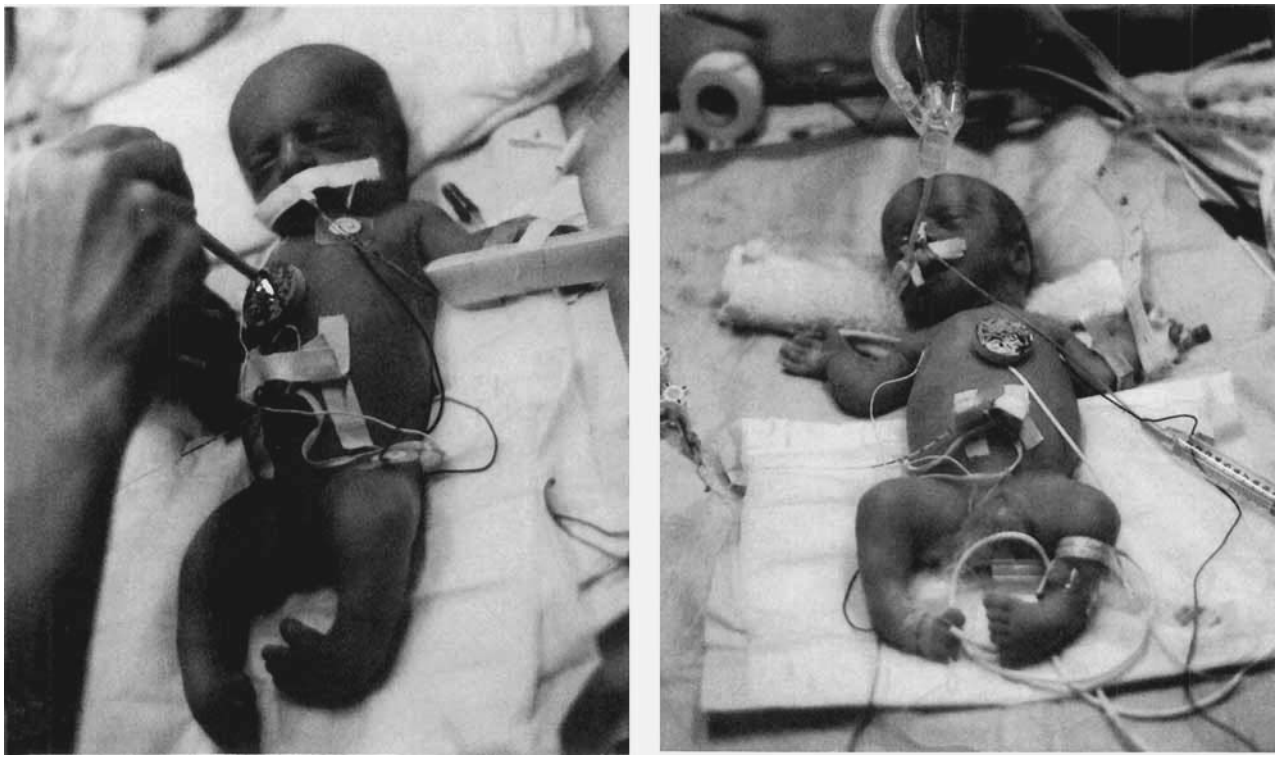

Fig. 2. Female twins (MZ). Patient 2 (**left**) and patient 3 (**right**). Note talipes equinovarus, short limbs, prominent foreheads, and micrognathia.

Fig. 3. Patient 2 at age 2 months when left ear cyst developed.

Fig. 4. Patient 2 at age 2 months with absent proximal flexion crease of second finger. Both third and fourth fingers had clinocamptodactyly, which is obscured by artificial extension of fingers.

Molecular studies on the distal 5q region by Dr. Johanna Hästbacka of the University of Helsinki on the parents and 3 affected sibs are not yet completed; essentially, the type and location of mutation in this family could be informative concerning the variability in this sibship.

Diagnosis of diastrophic dysplasia is usually straightforward, but variable expression can result in a mild phenotype which at one time would have been considered a "variant" [Lachman et al., 1981]. The present

Fig. 5. Neonatal radiograph of patient 1. Note thin ribs, short ilial base, mildly wide metaphyses, absent proximal femoral epiphyses, short femoral necks, and short bowed femurs.

family suggests that some cases are milder because individual traits are less fully expressed and/or a number of the more common ones are absent; making a secure diagnosis of diastrophic dysplasia is not always possible. Diagnosis in such cases is hampered by the nonspecific radiological findings in diastrophic dysplasia. The hand findings offer the greatest specificity when compared to the other radiological traits of diastrophic dysplasia, and this sibship, particularly the boy, did not have the typical specific anomalies of irregularly contoured phalanges and metacarpals and short/ovoid first metacarpals. Long-term follow-up and regularly repeated radiographs may clarify such cases. Occasionally, rib or iliac crest biopsy for histopathological diagnosis may be necessary. Molecular studies will eventually clarify the diagnosis in questionable cases [Hastbacka et al., 1990].

TABLE IV. Radiological Anomalies in a Sibship With Diastrophic Dysplasia

	Male, patient 1	Female, twin A, patient 2	Female, twin B, patient 3
Short/broad/bowed long bones	+	+	+
Wide metaphyses	+	+	+
Brachydactyly	+ (regular)	++ (regular)	++ (regular)
Short iliac base	+	+	+
Short femoral necks	+	+	+
Spine (scoliosis/kyphosis)	− (later lordotic)	−	−

Fig. 6. Radiograph of upper arms and forearms at age 10 months of patient 1. Note short, thick humeri with wide metaphyses and mildly bowed radii.

Fig. 7. Roentgenogram of lower limbs at age 10 months of patient 1. The bones are short and bowed with wide metaphyses, short femoral necks, and relatively normal ossified distal femoral epiphyses.

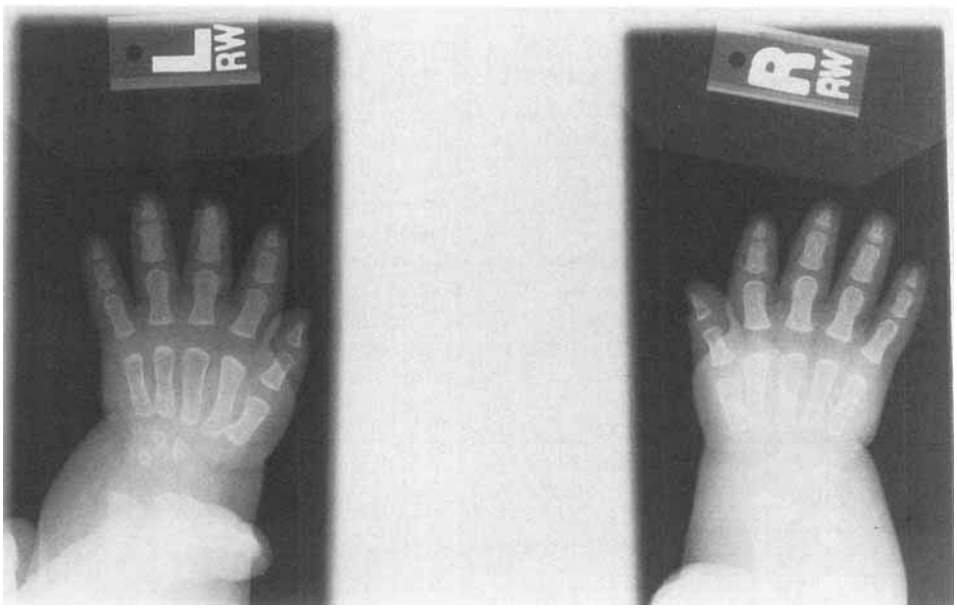

Fig. 8. Hand films of patient 1 at age 10 months. Note generalized brachydactyly with relatively normal (regular) contour to phalanges and metacarpals. Note that first metacarpal is not disproportionately short or ovoid in contour.

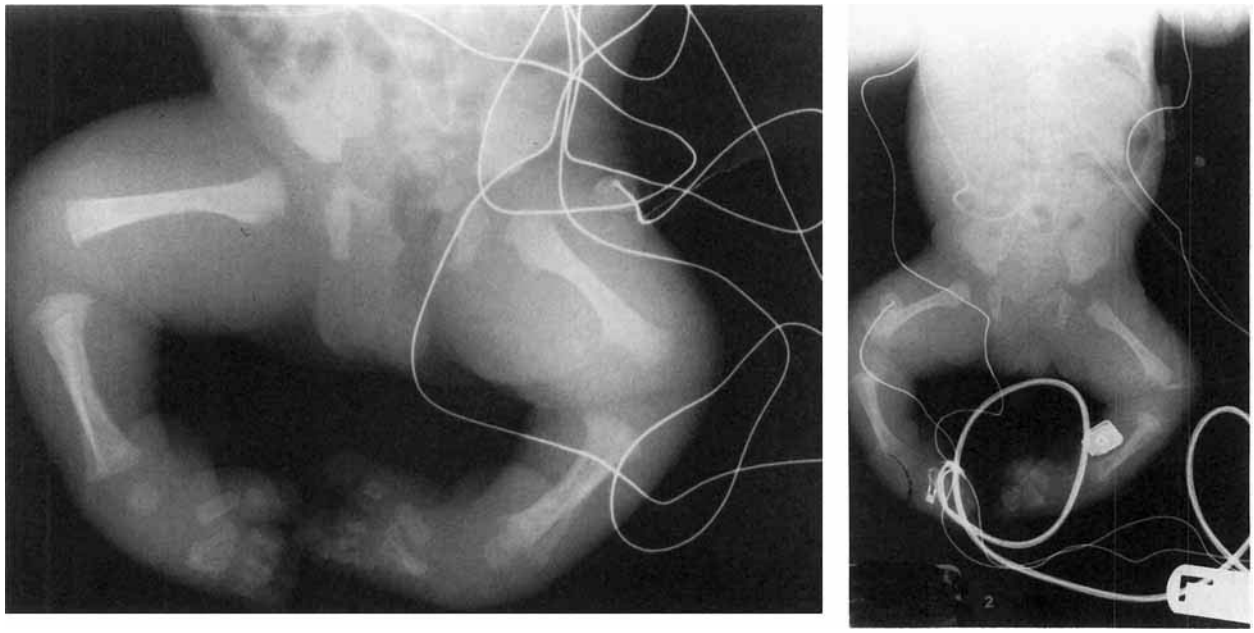

Fig. 9. Neonatal hip and lower limb films of patient 2 (**left**) and patient 3 (**right**). Note short ilial base, short femoral necks, short bowed long bones, and wide metaphyses.

Fig. 10. Hand radiogram of patient 3 during neonatal period. Note somewhat more severe generalized brachydactyly than found in patient 1 (Fig. 8); the phalanges and metacarpals, however, maintain a regular contour and the first metacarpal is not ovoid in shape.

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